52. (New) A vector which comprises the DNA sequence of claim 49.

53. (New) A vector which comprises the DNA sequence of claim 50.

54. (New) A host cell transformed with the vector of claim 51.

55. (New) A host cell transformed with the vector of claim 52.

56. (New) A host cell transformed with the vector of claim 53.

57. (New) A secreted human thyroid peroxidase produced from the DNA sequence of claim 48.

REMARKS

Claims 11 to 15 are pending but rejected. Claims 11 to 15 are presently canceled without prejudice. Claims 37 has been withdrawn from consideration. Claims 38 to 57 are newly added.

The key limitation of Claims 38 to 47 is that the human thyroid peroxidase mentioned therein is recognized by a disease associated antibody, for example antibodies found in the serum of Hashimoto patients. The key limitation of Claims 48 to 57 is that the human thyroid peroxidase mentioned therein is (1) secreted and (2) recognized by a disease associated antibody. Claims 38 to 57 are supported by Example XI (Specification, pp. 48-60). The specification, at p. 58, lines 6-8 states: "As a consequence of the mutation, a 'truncated' human thyroid peroxidase protein is expressed which is secreted by the host cell rather than bound to its membrane". A specific example of the vector of claims 48 to 50 and 58 to 60 is disclosed in the specification, p. 58, lines 16-21. Specific examples of the host cells of claims 51 to 53 and 61 to 63 are CHO-TPO-MI-K cells. The first full paragraph of p. 59 of the specification discloses the testing of the secreted human thyroid peroxidase (hereinafter referred to as "hTPO") for its ability to immunoprecipitate human anti-hTPO antibodies in Hashimoto's serum and the result was

illustrated in Figure 14B. As expected in the "Brief Description of the Drawings", Figure 14B shows the "Immunoprecipitation of mutated hTPO from clones of CHO-TPO-MI-K cells generated by limiting dilution. Immunoprecipitations were performed with serum from a patient with Hashimoto's thyroiditis with high anti-hTPO antibody levels. The specificity of the immunoprecipitation is shown by the inability of serum from a normal individual (CON) to precipitate the 105-101 kD doublet." (Specification, p. 14, first full para.).

Rejection under 35 U.S.C. §103

Applicants respectfully submit that these new claims as drafted overcome the previously cited rejection under 35 U.S.C. §103. The claims cannot be rejected if the prior references or the combination of prior references do not show that there was a reasonable expectation of success that a recombinant DNA could encode a truncated hTPO that may be recognized by antibodies associated with a disease, for example Hashimoto's disease. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).

An antibody recognizes a protein by the protein's very specific three dimensional structure. Therefore, to predict with any likelihood of success that an antibody will recognize a particular protein, the first task is to be able to determine what the three dimensional structure of that protein may be. However, *protein chemistry is very unpredictable and the three dimensional conformation of a protein may unpredictably change upon alterations to the primary amino acid sequence of the protein.* There is no reference at the time of the invention teaching that it is possible to predict with any certainty the three dimensional structure of a protein from its primary structure. In fact at about the same time as the filing of this application, Bowie et al. published an article stating to the contrary. Bowie et al. stated that to "predict structure from sequence...and subsequently to infer detailed aspects of function from the structure...[is] extremely complex, and it seems unlikely that either will be solved in an exact manner in the near future." *Science* (March 1990) **247**: 1306-1310 at 1306 col. 1). Furthermore, Wadsworth et al. reported that a single amino acid alteration to a thyroid stimulating hormone receptor

completely alters its function, implicating that its three dimensional structure changes with the single amino acid alteration. *Molecular Endocrinology* **6**: 394-398 (1992).

In view of the above discussion, Applicants respectfully submit that Claims 38 to 57 are nonobvious and that such Claims have overcome the Examiner's rejection.

Respectfully submitted,

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